



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>C12N 5/06, A61K 38/22, 38/26, C07K</b> <b>14/605, 14/575, A61P 5/50</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 00/09666</b> <b>(43) International Publication Date:</b> 24 February 2000 (24.02.00)
<b>(21) International Application Number:</b> PCT/US99/18099 <b>(22) International Filing Date:</b> 10 August 1999 (10.08.99) <b>(30) Priority Data:</b> 60/095,917 10 August 1998 (10.08.98) - US <b>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application</b> US 60/095,917 (CON) Filed on 10 August 1998 (10.08.98) <b>(71) Applicant (for all designated States except US):</b> THE GOVERNMENT OF THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; National Institutes of Health, Office of Technology Transfer, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852-3804 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> EGAN, Josephine [US/US]; 2421 Everton Road, Baltimore, MD 21209 (US). PERFETTI, Riccardo [US/IT]; 1729 Corcoran Street, N.W., Washington, DC 20009 (US). PASSANITI, Antonino	[US/US]; 18315 Peters Avenue, White Hall, MD 21161 (US). GREIG, Nigel [US/GB]; 14415 Long Green Drive, Silver Springs, MD 20906 (US). HOLLOWAY, Harold [US/US]; 121 Mariners Point Drive, Middle River, MD 21220 (US). <b>(74) Agents:</b> SPRATT, Gwendolyn, D. et al.; Needle & Rosenberg, P.C., The Candler Building, Suite 1200, 127 Peachtree Street, N.E., Atlanta, GA 30303-1811 (US). <b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). <b>Published</b> <i>With international search report.</i> <b>(88) Date of publication of the international search report:</b> 23 November 2000 (23.11.00)	
<b>(54) Title:</b> DIFFERENTIATION OF NON-INSULIN PRODUCING CELLS INTO INSULIN PRODUCING CELLS BY GLP-1 OR EXENDIN-4 AND USES THEREOF		
<b>(57) Abstract</b> <p>The present invention relates to a population of insulin producing cells made by a process comprising contacting non-insulin producing cells with a growth factor selected from the group consisting of GLP-1 or Exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1 or Exendin-4, and fragments thereof. The present invention also relates to methods of differentiating non-insulin producing cells into insulin producing cells and of enriching a population of cells for insulin-producing cells. The present invention also relates to methods of treating diabetes.</p>		

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# INTERNATIONAL SEARCH REPORT

Inter. Application No

PCT/US 99/18099

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N5/06 A61K38/22 A61K38/26 C07K14/605 C07K14/575  
A61P5/50

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MASHIMA ET AL: "FORMATION OF INSULIN-PRODUCING CELLS FROM PANCREATIC ACINAR AR42J CELLS BY HEPATOCYTE GROWTH FACTOR" ENDOCRINOLOGY, vol. 137, no. 9, 1996, pages 3969-3976, XP000670297 ISSN: 0013-7227 cited in the application	31
A	abstract; figure 8 page 3974, left-hand column page 3975, right-hand column ---	1,2,4-6, 9,12,13, 15-17, 20,23, 25,27, 29,32,33
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

15 June 2000

Date of mailing of the international search report

21. JUNE 2000

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# INTERNATIONAL SEARCH REPORT

Inter. Appl. Application No

PCT/US 99/18099

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 31214 A (LONDON HEALTH ASS ; DUPRE JOHN (CA)) 23 November 1995 (1995-11-23) page 1, line 31 - line 34 page 2, line 32 - page 3, line 20 page 4, line 26 - line 30 ----	34
X	US 5 424 286 A (ENG J) 13 June 1995 (1995-06-13) abstract ----	36
A	GEFEL ET AL: "GLUCAGON-LIKE PEPTIDE-I ANALOGS: EFFECTS ON INSULIN SECRETION AND ADENOSINE 3',5'-MONOPHOSPHATE FORMATION" ENDOCRINOLOGY, vol. 126, no. 4, 1990, pages 2164-2168, XP000574862 ISSN: 0013-7227 ----	
A	THORENS B ET AL: "CLONING AND FUNCTIONAL EXPRESSION OF THE HUMAN ISLET GLP-1 RECEPTOR DEMONSTRATION THAT EXENDIN-4 IS AN AGONIST AND EXENDIN-(9-39) AN ANTAGONIST OF THE RECEPTOR" DIABETES, vol. 42, no. 11, 1 November 1993 (1993-11-01), pages 1678-1682, XP000571435 ISSN: 0012-1797 cited in the application ----	
E	WO 99 43705 A (NOVONORDISK AS) 2 September 1999 (1999-09-02) abstract -----	34

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 99/18099

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —  
because they relate to subject matter not required to be searched by this Authority, namely:  
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy  
Although claims 34-52 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 99/18099

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

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- ☐ The additional search fees were accompanied by the applicant's protest.
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-11, 23-26, 31, 32, 34, 35, 39-52

A method of differentiating non-insulin producing cells into insulin producing cells by contacting the cells with a growth factor, cells produced by the method and uses of the method or the cells for treating subjects diagnosed with type 1 diabetes, where the growth factor is GLP-1, peptides substantially homologous to GLP-1 or fragments thereof.

2. Claims: 12-22, 27-30, 33, 36-38

A method of differentiating non-insulin producing cells into insulin producing cells by contacting the cells with a growth factor, cells produced by the method and use of the method for treating subjects diagnosed with type 1 diabetes, where the growth factor is Exendin-4, peptides substantially homologous to Exendin-4 or fragments thereof.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 34-52 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy



# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 99/18099

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 9531214 A	23-11-1995	AU 711611 B	14-10-1999
		AU 2404495 A	05-12-1995
		CA 2190112 A	12-05-1995
		EP 0762890 A	19-03-1997
		JP 10500114 T	06-01-1998
US 5424286 A	13-06-1995	NONE	
W0 9943705 A	02-09-1999	AU 2610599 A	15-09-1999

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